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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/928,757	09/12/97	MAERTENS G	1487-17

HM12/1115

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EXAMINER	
ZEMAN, M	
ART UNIT	**PAPER NUMBER**
1631	15

DATE MAILED: 11/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/928,757	MAERTENS ET AL.	
	Examiner	Art Unit	
	Mary K Zeman	1631	

-- The MAILING DATE of this communication appears on the cov r sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *24 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-51,53 and 55-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-51,53 and 55-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☒ received in Application No. (Series Code / Serial Number) *08/612,973* .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 8/24/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/928757 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's arguments filed 8/24/00 have been fully considered but they are not persuasive. All non-reiterated rejections have been withdrawn.

Claims 59-51, 53 and 55-64 are pending in this application.

Specification

The disclosure is objected to because of the following informalities: The tables at pages 68-70 and 72 of the specification were not carefully copied from the original. The information from the far left side of the tables (at the bottom of the pages) is illegible. Applicant is requested to provide substitute pages that clearly contain all the relevant information.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-51, 53 and 55-56 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous office action..

No new arguments regarding the rejection set forth 7/24/00 have been entered. Applicant maintains that the application fully enables the claims as filed. Applicant has not specifically addressed the reasons and questions set forth in the Final Rejection of 7/24/00. Applicant's arguments and supporting documents have been fully considered. Applicant asserts that HCV

peptide vaccines, in fact, are useful as prophylactic vaccines, when they contain T cell stimulating epitopes. Applicant further argues that given the disclosures of Farci, Choo, Maertens, and Rosa, that one of skill in the art would recognize the workability of E1 or E2 peptide vaccines for HCV. These arguments have been fully considered, but are not persuasive.

As set forth previously, the specification is devoid of working examples demonstrating protection from viral challenge in a reasonable model system using any of the polypeptides of the invention. The area of protective vaccines, and the elicitation of protective immunity in HCV is highly unpredictable, as demonstrated by Farci (1992) and its contradictions with other art, such as the art cited by applicant.

Applicant submits Farci (1996) in support of his position. Farci (1996) vaccinated chimpanzees with polypeptides of E1. While some neutralizing antibodies were elicited to those peptides, escape mutants arose, and resulted in HCV infection of the animals. This is not the elicitation of a protective response, and is not a demonstration of an effective vaccine. Further, Applicant has not indicated, or even suggested that the peptides of Farci (1996) are the same as, or similar to the peptides of the invention, nor is it clear that the peptides of Farci (1996) contain a T cell stimulating epitope, as required by the invention.

In regards to Choo et al (1994), Choo vaccinates the chimpanzees with full length E1/E2 complexes. The polypeptides of the invention are not all full length, not necessarily in complex with one another, and not necessarily from the same subtype as that of Choo et al. Determination of the elements required to match the results of Choo, using smaller peptides, remains unpredictable. And while Choo obtained protection in some animals, at least two animals became infected with HCV upon viral challenge. This is not evidence that the claimed polypeptides can provide protective immunity in response to challenge virus. Applicant's polypeptides are quite different from the immunogens used by Choo et al, such that one cannot automatically draw the same conclusions for Applicant's polypeptides. It is entirely unclear whether the individual polypeptides of the invention would function in the same manner as full length E1/E2 complexes.

Rosa (1996) discloses a test which estimates the levels of neutralizing antibodies to particular polypeptides of HCV. The presence of neutralizing antibodies is not a reliable indication of a protective immune response. Rosa uses full length E1, and a truncated E2

(aa384-715), which is still larger than the polypeptides of the invention. Rosa concludes that vaccination with certain proteins of HCV can correlate with the elicitation of neutralizing antibodies, and that *more than one epitope* on E2 is required for these effects. Again, as the polypeptides of Rosa are significantly different than the polypeptides of the invention, one cannot automatically draw the same conclusions. It is not clear that the polypeptides of the invention possess both epitopes identified by Rosa as being important for the generation of neutralizing antibodies. Even if the peptides of the invention did possess those epitopes, there is no evidence that those neutralizing antibodies are protective in an *in vivo* situation.

Applicant has submitted two abstracts by the inventors, describing vaccine experiments using purified E1 protein. These experiments appear to have used full length E1 protein, and not the shorter polypeptides of the invention, thus the conclusions of Maertens cannot immediately be applied to the polypeptides of the invention. Further, the polypeptides of the invention are not limited to those purified by a particular method, or limited to any particular subtype of HCV such that no direct comparisons or conclusions can be made.

Diepolder (1997) submitted by Applicant, identifies a immunodominant polypeptide with T cell stimulating epitopes, however this epitope is not within E1 or E2, and Diepolder does not investigate vaccination and challenge experiments with that polypeptide. The relevance of Diepolder to the claimed invention (therapeutic vaccines) is unclear.

Finally, Botarelli (1993) investigates the T cell stimulating ability of 6 recombinant HCV proteins. Botarelli uses full length E1 and E2 proteins, and is unable to draw solid conclusions as to their T cell stimulating ability in the patients sampled. No conclusions as to protection from further infection are set forth by Botarelli.

Given the lack of success in the art, the lack of a correlation between the art and the invention, the lack of working examples in the specification, and the unpredictability of the generation of protective immunity, the specification, as filed, is not enabling for such vaccines.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 58 is rejected under 35 U.S.C. 102(b) as being anticipated by DeLeys (WO 93/18054).

Claim 58 is drawn to a composition comprising a peptide comprising at least one of a variety of peptides, including SEQ ID NO: 56, and 72 as representative examples.

DeLeys (WO 93/18054 16 September 1993) discloses a peptide which comprises the sequence of SEQ ID NO: 72. See attached alignment (Registry numbers 153299-61-7 and 153299-59-3 of DeLeys). DeLeys specifically contemplates using the peptides in therapeutic compositions and in immunogenic compositions (page 26).

Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Houghton et al. (EP 388232).

Houghton et al. (EP 388232 A1 19 September 1990) discloses an HCV peptide which comprise the sequence of SEQ ID NO: 56. See Attached Alignment of Registry Number: 133403-44-8 with SEQ ID NO: 56. Houghton et al. discuss at length the use of the peptides in compositions, immunogenic compositions, and therapeutic compositions throughout the specification.

Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Miyamura et al. (EP 537626).

Miyamura et al. (EP 537626 A1, 21 April 1993) discloses compositions comprising a peptide comprising the sequence of SEQ ID NO: 72. See attached Alignment with registry number 149119-56-2 (SEQ ID NO 10) of Miyamura et al. and claims 1-12.

Claims 57, 59-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Ralston et al. (USP 6,074,846).

Claims 57 and 59-64 are drawn broadly to compositions or therapeutic compositions of E1 or E2 proteins, and methods of administering those compositions to elicit HCV-specific antibodies. The instant specification (page 5, first full paragraph) indicates that the E1 or E2 proteins can be selected from any isolate or subtype of HCV.

Ralston et al (USP 6,074,846, having priority under 35 USC 120 to at least 5/1994) discloses purified compositions of E1 or E2 proteins and compositions of E1/E2 aggregates produced in mammalian yeast cells. The peptide compositions can be used in various applications, including as immunogens for the elicitation of specific antibodies (see for example, column 2 lines 53-58, column 8 lines 24-25, column 9 lines 1-65). The peptide compositions can further comprise carriers, diluents, and adjuvants.

Claims 57, and 59-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Brechot et al (USP 5,866,139).

Brechot et al. (USP 5,866,139) disclose compositions comprising purified HCV E1 polypeptides, and methods of using those peptides a immunogens to elicit specific antibodies. See claims 7-12, and SEQ ID NO: 3, 5 and 7 of Brechot et al..

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308 4028.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center receptionist whose telephone number is (703) 308-0196.

mkz
November 2, 2000

Examiner, 1631